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10/532,041	06/23/2006	Francois Schutze	032013-121	5818

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,041	SCHUTZE ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-9,15 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-9,15 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 11/20/2008, are acknowledged and entered. Claims 2, 5, 11, 14, and 18-20 have been cancelled by Applicant. Claims 1, 6-9, 15, and 21 are pending and under examination.

Response to Arguments

Any previous rejections and/or objections to claims 2, 5, 11, 14, and 18-20 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 is again rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitation "is comprised between" as recited in claim 6 is unclear when used in relation to the claimed weight ratio ranges. It is not clear whether it is Applicants' intent that the weight ratio be specifically between the claimed ranges, or whether the claimed ranges are only part of ("comprised") a broader range. Amending the claims to recite "is between" would overcome this rejection provided there is support in the specification for such an amendment.

Applicant's arguments have been carefully considered but they are not deemed persuasive. Applicants argue that claim 6 is amended to replace the phrase "is comprised between" with "is between". However, no such amendment to claim 6 was made. Accordingly, the rejection is maintained for the reasons of record and as reiterated above.

The rejection of claims 9 and 20 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention regarding the limitation "is administrable via the oral or the

parenteral route", is **withdrawn** in light of Applicant's amendments to claim 9 and cancellation of claim 20.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-9, 15, and 21 are again rejected under 35 U.S.C. 103(a) as being unpatentable over **Brulls** (USP No. 6,730,685 B1; Issued May 4, 2004; Filed Oct. 13, 2000) in view of **Mangel *et al.*** (WO 01/56573 A1; Published August 9, 2001).

Brulls teaches pharmaceutical compositions that are combinations of tenatoprazole and other drug treatments, such as "a motility stimulating drug" (column 7, lines 22-26). Tenatoprazole is exemplified as a compound of Formula I at the top of column 12. Brulls' teaching is drawn to treatment of diseases relating to gastric hyperacidity, such as gastric and duodenal ulcers and reflux esophagitis (columns 6-7 under Use of the Invention). A dosage range for tenatoprazole is taught to be 1-100 mg once or twice a day (column 7, lines 14-15), thus suggesting the amount of tenatoprazole as recited in claim 7 and claim 15. Both oral and parenteral administration is disclosed in column 3, lines 1-8, thus teaching the limitations of claim 9. As required by instant claim 8, sodium or potassium salts are disclosed in claims 4 and 5. Brulls is silent with respect to the disclosed "motility stimulating drug".

However, Mangel *et al.* teach using COX-2 inhibitors for the treatment of disorders ameliorated by a gastroprokinetic, based on the discovery that COX-2 inhibitors stimulate gastrointestinal motility (Abstract; page 1, lines 29-30). Celecoxib (as elected by Applicants) is among the COX-2 inhibitors disclosed for use in the invention taught in Mangel *et al.* (page 5, line 7; page 7, line 14; page 8, line 4). With respect to tenatoprazole, Mangel *et al.* teach that it may be advantageous to administer other therapeutic agents in combination with a COX-2 inhibitor (page 8, lines 10-12); among such agents are proton pump inhibitors, specifically tenatoprazole (page 8, lines 15-17). With respect to the dose of celecoxib as recited in claims 7 and 15, Mangel *et al.* suggest effective doses of the COX-2 inhibitors of the invention are 0.01 to 500 mg, preferably 0.05 to 250 mg, for example 0.5 to 100 mg per unit dose (page 11, lines 8-11). With respect to compositions being administrable via the oral or the parenteral route as recited in claim 9, Mangel *et al.* teach that the compositions of the invention can be formulated for oral or parenteral administration (page 9, lines 9-15).

Brulls and Mangel *et al.* thus suggest and motivate combining a "motility stimulating drug" (*e.g.*, celecoxib) with a proton pump inhibitor (*e.g.*, tenatoprazole).

Brulls and Mangel *et al.* differ from the compositions as recited in the instant claims in that they do not disclose the weight ratio of tenatoprazole to anti-inflammatory agent (*e.g.*, celecoxib) as recited in claim 6. However, it would have been obvious to one of ordinary skill in the art at the time of the invention that the ratio of tenatoprazole to celecoxib could be readily adjusted in order to formulate a composition for the treatment of diseases ameliorated by a gastroprokinetic as suggested by Mangel *et al.* Such optimization of a prior art composition suggested by the prior art is well within the purview of the skilled artisan and could be achieved through routine experimentation. It is not inventive to discover an optimum or workable range by routine experimentation when general conditions of a claim are disclosed in the prior art. See *In re Aller*, 105 USPQ 233,235 (CCPA 1955) and MPEP 2144.05(II). The currently claimed specific weight ratio ranges are not seen to be inconsistent with ranges that would have been readily determined by the skilled artisan via routine optimization.

Applicant's arguments have been carefully considered but they are not deemed to be persuasive. Applicants note that the present claims are directed to a pharmaceutical composition comprising an anti-inflammatory agent selected from a NSAID or a cyclooxygenase-2 inhibitor,

in combination with tenatoprazole. The Examiner agrees with Applicant's characterization of the claimed invention. Applicant argues that the concomitant administration of a proton pump inhibitor [tenatoprozole] does not fully meet the need for preventative therapy (i.e., to prevent the adverse effects associated with the use of anti-inflammatory drugs). However, Applicants are respectfully reminded that the instant claims are composition claims, not method claims. As such, the intended use of the composition is not pertinent to the present rejection. The cited prior art teaches, suggests, and motivates combining a COX-2 inhibitor such as celecoxib with a proton-pump inhibitor such as tenatoprozole, which is the same composition recited in the claims. As such, it is not seen by the Examiner how the composition suggested and motivated by the prior art "does not fully meet the need for preventative therapy" because the composition suggested by the prior art is the same as that claimed by Applicants.

Secondly, Applicants argue that the studies performed with the present invention show that the combination of tenatoprazole and an anti-inflammatory agent selected from those recited in the claims achieves unexpected benefits and uses when compared with other PPIs and with anti-inflammatories used alone or in combination. As a first matter, there is no study in the present invention comparing tenatoprazole with other PPIs in combination with the claimed anti-inflammatory agents. Table 2 demonstrates that tenatoprazole in combination with anti-inflammatory agents reduces digestive disorders, however this is an expected result in view of the teachings of the cited prior art. Applicants go on to discuss the pharmacokinetic features of tenatoprazole, such as elimination half-life, tissue exposure, AUC, etc. and argue that such features differ from those of other PPIs. However, the pharmacokinetic parameters of tenatoprazole are inherent characteristics of the drug and thus administration of the drug will necessarily have these pharmacokinetic features. Such features are not dependent on its administration with an anti-inflammatory drug. As such, the pharmacokinetic characteristics of tenatoprazole are not deemed an unexpected result resulting from the claimed combinations.

Thirdly, Applicants argue that Brulls fails to disclose ant particular NSAID or any particular combination of one PPI with a NSAID. However, as discussed above, Brulls discloses combinations of tenatoprazole and other drug treatments, such as "a motility stimulating drug" (column 7, lines 22-26). Mangel *et al.* teach that it may be advantageous to administer other therapeutic agents in combination with a COX-2 inhibitor (page 8, lines 10-12), which is

disclosed to stimulate gastrointestinal motility (Abstract; page 1, lines 29-30) ; among such agents are proton pump inhibitors, specifically tenatoprazole (page 8, lines 15-17). As such, the combined teachings of the cited prior art suggest and motivate pharmaceutical compositions comprising a COX-2 inhibitor such as celecoxib and tenatoprazole. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Accordingly, the claims are deemed properly rejected for the reasons of record and as reiterated above.

Claims 1, 6-7, 9, 15, and 21 are again rejected under 35 U.S.C. 103(a) as being unpatentable over **Chih-Ming *et al***. (WO 02/22108 A1; Published March 21, 2002) in view of **Mangel *et al***. and **Naesdal *et al***. (European Journal of Gastroenterology and Hepatology, 2001, vol. 13, pages 1401-1406).

Chih-Ming *et al*. teach oral solid dosage forms containing a non-steroidal anti-inflammatory drug (NSAID) and a proton pump inhibitor effective to inhibit or prevent gastrointestinal side effects normally associated with the NSAID (Abstract). With respect to NSAIDs, Chih-Ming *et al*. teach that "NSAID" refers to "any compound acting as a non-steroidal anti-inflammatory agent identifiable as such by one of ordinary skill in the art" (page 9). With respect to tenatoprazole, Chih-Ming *et al*. teach that any proton-pump inhibitor may be used in the invention disclosed therein, but they do not explicitly recite the claimed tenatoprazole (pages 10-11). However, the inventors do suggest that isomers, enantiomers, tautomers, and alkaline salts of proton pump inhibitors may be used (page 11), and that the compositions comprising a NSAID and proton pump inhibitor is administered orally (page 12). In preferred examples, the weight ratio of proton pump inhibitor to NSAID is about 1:10 or 1:5, thus suggesting the limitations of claims 6, 11, and 14 (pages 27-31)

Chih-Ming *et al*. differ from the instant claims in that they do not specify tenatoprazole as a proton-pump inhibitor of the invention and they do not teach that the NSAID can be celecoxib.

However, Mangel *et al.*, as discussed *supra*, teach that it may be advantageous to administer other therapeutic agents in combination with a COX-2 inhibitor (page 8, lines 10-12); among such agents are proton pump inhibitors, specifically tenatoprazole (page 8, lines 15-17).

Further, Naesdal *et al.* provide additional motivation to administer a proton pump inhibitor to patients being treated with a COX-2-selective NSAID. In this regard, Naesdal *et al.* teach that while COX-2-selective NSAIDs are associated with a lower risk of ulceration than non-selective NSAIDs, comparable proportions of NSAID users report upper gastrointestinal symptoms regardless of COX- selectivity (Abstract; page 1404, right column)). The authors thus suggest that a proton pump inhibitor should be considered for prevention of ulceration associated with NSAID use (id.).

Accordingly, in view of the cited prior art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine tenatoprazole and celecoxib in a pharmaceutical composition. As discussed *supra*, Chih-Ming *et al.* suggest and motivate the combination of a NSAID and a proton-pump inhibitor generally, although they do not explicitly teach the claimed tenatoprazole and celecoxib. However, tenatoprazole was a well-known proton-pump inhibitor at the time of the invention as evidenced by Mangel *et al.* and thus one skilled in the art would recognize that tenatoprazole would be useful as a proton-pump inhibitor in the invention disclosed in Chih-Ming *et al.* With respect to celecoxib, although the prior art recognizes that use of celecoxib is accompanied by fewer gastrointestinal side effects when compared to non-selective NSAIDs (see Naesdal *et al.*), the prior art also suggests that proton pump inhibitors should be considered for prevention of ulceration associated with NSAID use generally (*id.*). As such, the skilled artisan would have been imbued with at least a reasonable expectation that a pharmaceutical composition comprising tenatoprazole and celecoxib would be useful in the treatment of pain and inflammation and would potentially result in fewer gastrointestinal side effects as suggested by Chih-Ming *et al.* in view of Mangel *et al.* and Naesdal *et al.*

Applicants' arguments have been carefully considered but they are not persuasive. Applicants argue that Chih-Ming does not provide a specific combination of active ingredients but instead provides a new dosage form. However, the new dosage form taught in Chih-Ming contains a non-steroidal anti-inflammatory drug (NSAID) and a proton pump inhibitor effective

to inhibit or prevent gastrointestinal side effects normally associated with the NSAID. While Chih-Ming do not explicitly disclose celecoxib and tenatoprazole as suitable NSAID and protein pump inhibitor, respectively, celecoxib was a known NSAID and tenatoprazole was a known proton pump inhibitor as evidenced by the cited prior art. As such, there is nothing unobvious about using these agents in the new dosage form disclosed in Chih-Ming, which is taught to inhibit or prevent gastrointestinal side effects normally associated with the NSAID.

Accordingly, the claims are deemed properly rejected for the reasons of record and as reiterated above.

Claims 1, 6-9, 15, and 21 are again rejected under 35 U.S.C. 103(a) as being unpatentable over **Chih-Ming *et al.***, **Mangel *et al.***, **Naesdal *et al.*** as applied to claims 1, 6-7, 9, 15, and 21 above, and further in view of **Bergstrand *et al.*** (USP No. 5,753,265; Issued May 19, 1998).

Chih-Ming *et al.*, Mangel *et al.*, and Naesdal *et al.* teachings are discussed supra and are applied herein in the same manner and in their entirety. Claim 8 differs from Chih-Ming *et al.*, Mangel *et al.*, and Naesdal *et al.* in that the references do not disclose the specific alkaline salts of tenatoprazole recited in the claim.

However, Bergstrand *et al.* teach pharmaceutical preparations containing an acid labile H^+K^+-ATPase inhibitor or an alkaline salt thereof (Abstract). Tenatoprazole is one such acid labile H^+K^+-ATPase inhibitor as disclosed at column 3, lines 20-25. The alkaline salts recited in instant claim 8 are taught at column 3, lines 36-39. The compounds of the invention are taught to be useful in inhibiting gastric acid secretion in mammals and for the treatment of gastrointestinal disorders where gastric acid inhibitory effect is desirable, *e.g.*, in patients on NSAID therapy (*id.* at lines 44-52).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use an alkaline salt of tenatoprazole in the pharmaceutical formulations suggested by the cited prior. The motivation to do so is found in Bergstrand *et al.*, who teach that such alkaline salts are useful in pharmaceutical preparations for the treatment of gastrointestinal disorders.

Applicants' arguments have been carefully considered but they are not deemed persuasive. Applicants argue that Bergstrand does not cure the "deficiencies" of Chih-Ming,

Mangel, and Naesdal. However, as discussed above, Chih-Ming, Mangel, and Naesdal teach, suggest, and motivate pharmaceutical compositions comprising a NSAID such as celecoxib and a proton pump inhibitor such as tenatoprazole. Bergstrand is only provided as evidence that the alkaline salts of tenatoprazole as recite in claim 8 were known in the art at the time the invention was made.

Accordingly, the claims are deemed properly rejected for the reasons of record and as reiterated above.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
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